

Claims

This listing of claims will replace all prior versions:

1. (withdrawn) A method for inhibiting proliferation (DNA synthesis) of human fibroblasts comprising utilizing inhibitors of dipeptidyl peptidase IV (DP IV) as well as of inhibitors of enzymes having an equal substrate specificity (DP IV-analogous enzyme activity) or/and of inhibitors of alanyl aminopeptidase (aminopeptidase N, APN) as well as of inhibitors of enzymes having an equal substrate specificity (APN-analogous enzyme activity) for an inhibition of the proliferation (DNA synthesis) of human fibroblasts.
2. (withdrawn) The method according to claim 1, wherein the DP IV inhibitors are Xaa-Pro-dipeptides (Xaa= α -amino acid or side chain-protected derivative), corresponding derivatives, more preferably dipeptide phosphonic acid diaryl esters, dipeptide boronic acids (e.g. Pro-Boro-Pro) and their salts, Xaa-Xaa-(Trp)-Pro-(Xaa)_n peptides (Xaa= α -amino acid, n=0 to 10), corresponding derivatives and their salts, amino acid (Xaa) amides, corresponding derivatives and their salts, wherein Xaa represents an α -amino acid or a side chain-protected derivative, preferably N^ε-4-nitrobenzyl-oxycarbonyl-L-lysine, L-proline, L-tryptophane, L-isoleucine, L-valine, and cyclic amines, for example pyrrolidine, piperidine, thiazolidine and their derivatives, represent the amide structure, and/or tryptophane-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives (TSL) and (2S, 2S', 2S'')-2-[2'-(2''-amino-3''-(indole-3'''-yl)-1''-oxopropyl-)]1',2',3',4'-tetrahydro-6',8'-dihydroxy-7-methoxy-isoquinol-3-yl-carbonylamino-] 4-hydroxymethyl-5-hydro-pentanoic acid (TMC-2A).
3. (withdrawn) The method according to claim 1, wherein amino acid amides, preferably N^ε-4-nitrobenzyloxycarbonyl-L-lysine thiazolidide, pyrrolidide and piperidide as well as the corresponding 2-cyanothiazolidide, 2-cyanopyrrolidide and 2-cyanopiperidide derivative are used as the DP IV inhibitors.
4. (withdrawn) The method according to claim 1, wherein the inhibitors of APN are actinonin, leuhistin, phebestin, amastatin, bestatin, probestin, β -amino thiols, α -amino phosphinic acids, α -amino phosphinic acid derivatives, preferably D-Phe- ψ -[PO(OH)--CH₂]-Phe-Phe and their

salts.

5. (currently amended) A method ~~utilizing the inhibitor combinations according to claim 1 for a prevention and~~ for therapy in an individual in need of treatment for ~~of~~ benign fibrotic and sclerotic diseases (~~in particular~~ post-infectious and post-traumatic: hypertrophic scars, keloids, dermatofibroms, fibrolipomes, disseminated (myo-) fibromatoses), ~~as well as of~~ or malign fibroblast hyperproliferation states (~~for example~~ fibrosarcomes, mixed tumors as atypical fibroxanthoma, malign fibrous histiocytoma, aggressive angiomyxoma, paraneoplasiae), ~~of~~ or fibrotic autoimmune diseases ~~as, for example,~~ sclerodermia (circumscript sclerodermia, progressive-systemic sclerodermia, CREST syndrome), ~~of~~ or dermatosclerosis accompanying other collagenoses and the graft-versus-host disease, ~~of~~ or vitiligo (white spot disease, Lichen sclerosus et atrophicus), ~~and of~~ or the heterogeneous group of pseudosclerodermiae (~~as, for example~~ the eosinophilic/proliferative fascitis, pseudosclerodermiae generated by exogeneous causes ~~as, for example,~~ toxic oil syndrome, silicosis, porphyriae, eosinophilic myalgia syndrome, popular mucinosis (Lichen myxo-edematosus) or Borrelia-associated fibrosis states), ~~of~~ or secondary sclerosis conditions ~~as, for example,~~ in the course of a stasis fibrosis accompanying chronic venous insufficiency or lipolymphedemas, or in a fibrotic progressive stage of patternal alopecia (alopecia androgenetica) and of rare localized fibroblast diseases (Dupuytren's disease, Ledderhose's disease, "knuckle pads", penile induration (Peyronie's disease, induratio penis plastica), comprising administering to the individual in need of the treatment an inhibitor according to claim 1, wherein the therapy comprises an inhibition of activation, DNA synthesis and proliferation of human fibroblasts.

6. (withdrawn) Pharmaceutical preparations, comprising inhibitors of dipeptidyl peptidase IV (DP IV) as well as inhibitors of enzymes having DP IV-analogous enzyme activity or/and inhibitors of alanyl aminopeptidase (aminopeptidase N, APN) as well as inhibitors of enzymes having APN-analogous enzyme activity, in combination with per se known carrier, additive and/or auxiliary substances.

7. (withdrawn) Pharmaceutical preparations according to claim 6, comprising, as the DP IV inhibitors, Xaa-Pro-dipeptides (Xaa= α -amino acid or side chain-protected derivatives),

corresponding derivatives, more preferably dipeptide phosphonic acid diaryl esters, dipeptide boronic acids (e.g. Pro-Boro-Pro) and their salts, Xaa-Xaa-(Trp)-Pro-(Xaa)_n peptides (Xaa=α-amino acid, n=0 to 10), corresponding derivatives and their salts, amino acid (Xaa) amides, corresponding derivatives and their salts, wherein Xaa represents an α-amino acid or a side chain-protected derivative, preferably N^ε-4-nitrobenzyloxycarbonyl-L-lysine, L-proline, L-tryptophane, L-isoleucine, L-valine, and cyclic amines, for example pyrrolidine, piperidine, thiazolidine and their derivatives, represent the amide structure.

8. (withdrawn) Pharmaceutical preparations according to claim 6, comprising, as the DP IV inhibitors, preferably amino acid amides, for example N-4-nitrobenzyl-oxycarbonyl-L-lysine thiazolidide, pyrrolidide and piperidide as well as the corresponding 2-cyanothiazolidide, 2-cyanopyrrolidide and 2-cyanopiperidide derivative.

9. (withdrawn) Pharmaceutical preparations according to claim 6, comprising, as the APN inhibitors, actinonin, leuhistin, phebestin, amastatin, bestatin, probestin, β-amino thiols, α-amino phosphinic acids, α-amino phosphinic acid derivatives, preferably D-Phe-ψ-[PO (OH)--CH₂] - Phe-Phe and their salts.

10. (withdrawn) Pharmaceutical preparations according to claim 6, comprising two or several inhibitors of DPIV or inhibitors of enzymes having a DPIV-analogous enzyme activity or/and inhibitors of APN or inhibitors having an APN-analogous enzyme activity in a spacially separated formulation in combination with per se known carrier, auxiliary and/or additive substances for a simultaneous or, with respect to time, immediately consecutive administration with the aim of a joint effect.

11. (withdrawn) Pharmaceutical preparations according to claim 6 for a systemic application for an oral, transdermal, percutaneous, intravenous, subcutaneous, intracutaneous, intramuscular, rectal, vaginal, sublingual application together with per se known carrier, auxiliary and/or additive substances.

12. (withdrawn) Pharmaceutical preparations according to claim 6 for a topical application in the

form of creams, ointments, pastes, gels, solutions, sprays, liposomes or nanosomes, "pegylated" formulations, degradable depot matrices, mixable lotions, hydrocolloid dressings, plasters, microsponges, prepolymers or other dermatological bases/vehicles including instillative application.

13. (currently amended) A method for ~~the therapy and prevention~~ of dermatological diseases including a hyperproliferation and changed differentiation states of fibroblasts, comprising ~~the administration of~~ administering to an individual in need of the therapy inhibitors of dipeptidyl peptidase IV (DPIV) as well as of inhibitors of enzymes having an equal substrate specificity (DPIV-analogous enzyme activity) or/and of inhibitors of alanyl aminopeptidase (aminopeptidase N, APN) as well as of inhibitors of enzymes having an equal substrate specificity (APN-analogous enzyme activity), wherein the therapy comprises an inhibition of activation, DNA synthesis and proliferation of human fibroblasts.

14. (canceled)

15. (withdrawn) Pharmaceutical preparations according to claim 7 comprising two or several inhibitors of DPIV or inhibitors of enzymes having a DPIV-analogous enzyme activity or/and inhibitors of APN or inhibitors having an APN-analogous enzyme activity in a spacially separated formulation in combination with per se known carrier, auxiliary and/or additive substances for a simultaneous or, with respect to time, immediately consecutive administration with the aim of a joint effect.

16. (withdrawn) Pharmaceutical preparations according to claim 8, comprising two or several inhibitors of DPIV or inhibitors of enzymes having a DPIV-analogous enzyme activity or/and inhibitors of APN or inhibitors having an APN-analogous enzyme activity in a spacially separated formulation in combination with per se known carrier, auxiliary and/or additive substances for a simultaneous or, with respect to time, immediately consecutive administration with the aim of a joint effect.

17. (withdrawn) Pharmaceutical preparations according to claim 9, comprising two or several

inhibitors of DPIV or inhibitors of enzymes having a DPIV-analogous enzyme activity or/and inhibitors of APN or inhibitors having an APN-analogous enzyme activity in a spacially separated formulation in combination with per se known carrier, auxiliary and/or additive substances for a simultaneous or, with respect to time, immediately consecutive administration with the aim of a joint effect.

18. (new) The method of claim 13, wherein the inhibitor of DPIV is selected from Xaa-Pro-dipeptides (Xaa= α -amino acid or side chain-protected derivative) or a corresponding derivative selected from dipeptide phosphonic acid diaryl esters, dipeptide boronic acids and salts thereof, Xaa-Xaa-(Trp)-Pro-(Xaa)_n peptides (Xaa= α -amino acid, n=0 to 10) or a salt thereof, and amino acid (Xaa) amide or a salt thereof, wherein Xaa represents an α -amino acid or a side chain-protected derivative and wherein the amide is a cyclic amine.

19. (new) The method of claim 18, wherein the dipeptide boronic acid is Pro-Boro-Pro.

20. (new) The method of claim 18, wherein the α -amino acid or the side chain-protected derivative is selected from N^ε-4-nitrobenzyloxycarbonyl-L-lysine, L-proline, L-tryptophane, L-isoleucine, L-valine, and cyclic amines.

21. (new) The method of claim 18, wherein the cyclic amine is selected from pyrrolidine, piperidine, thiazolidine, tryptophane-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives (TSL) and (2S, 2S', 2S'')-2-[2'-(2''-amino-3''-(indole-3''-yl)-1''-oxopropyl)-1',2',3',4'-tetrahydro-6',8'-dihydroxy-7-methoxyisoquinol-3-yl-carbonylamino]-4-hydroxymethyl-5-hydro-pentanoic acid (TMC-2A).

22. (new) The method of claim 13, wherein the inhibitor of APN is selected from actinonin, leuhistin, phebestin, amastatin, bestatin, probestin, β -aminothiols, α -amino phosphinic acids, α -amino phosphinic acid derivatives.

23. (new) The method of claim 22, wherein the α -amino phosphinic acid derivative is selected from D-Phe- ψ -[PO(OH)--CH₂]-Phe-Phe salts thereof.

24. (new) The method of claim 13, wherein the inhibitor of DP IV is Lys[Z(NO₂)] thiazolidide.